Pathogenesis and management of arthropathy in cystic fibrosis

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Introduction

Approximately 80% of patients with cystic fibrosis (CF) now survive to the age of 13 years, and about 50% survive to the age of 20 years[1]. Increasing life expectancy has begun to highlight age-related complications of CF, and this includes the arthropathies associated with CF. These arthropathies have hitherto been given little attention in the literature, but recent estimates are that 7-8% of adolescents and adults with CF have some sort of symptomatic arthropathy other than simple finger-clubbing[2,3]. Although not common, joint disease in CF may be particularly disabling, due to the effects of both pain and reduced mobility.

A review of the literature[3-18] suggests that arthropathy may be associated with CF in three ways: (1) cystic fibrosis arthropathy (CFA), a complication characteristic of CF; (2) hypertrophic pulmonary osteoarthropathy (HPOA), familiar in other chronic respiratory disorders but previously thought to be uncommon in CF[13]; and (3) coincidental joint problems[8,16] such as juvenile rheumatoid arthritis[17].

We have treated 140 children under the age of 17 years with CF in the last six years. Three have had significant arthropathies with physical or radiological evidence of joint pathology. This does not include children who have complained of limb or joint pains in whom there were no objective signs of arthropathy. In addition, we have had the opportunity to investigate the arthropathy of 2 additional patients with CF. In this paper we report these 5 patients, and present our findings in conjunction with data culled from the 52 cases of CF and arthropathy in the literature[2-18]. All had the characteristic clinical features of CF and a sweat sodium concentration of greater than 70 mmol/l. The patients were divided, as above, into three groups: (1) CFA - 29 patients; (2) HPOA - 24 patients; and (3) other arthropathies - 4 patients. The division of cases was our own, and in a few instances did not coincide with the published allocation.

Cystic fibrosis arthropathy

Case 1: Presented with failure to thrive, steatorrhoea and recurrent respiratory infections, and CF was diagnosed at the age of 9 months. Onset of pain and swelling in knees and wrists occurred at the age of 8 years. The symptoms and signs lasted several days and then resolved without treatment. For the next three years, joint pain and swelling affecting the knees, wrists, fingers and ankles recurred every few months, lasted several days, and resolved spontaneously. The highest recorded ESR was 30 mm/h, the serum levels of IgA, IgG, IgM, uric acid, amylase were normal, and tests for rheumatoid factor, antinuclear antibodies, and antibodies to brucella and salmonella were negative. Later, aged 22, and during an arthritic relapse, the serum levels of IgG, IgA and IgM were normal, the C_3 was 0.84 g/l (normal 0.8-1.4) and the level of circulating immune complexes was 25 SP units (normal <20). Radiographs confirmed the presence of effusions in both knees, but showed no joint erosion or periosteal abnormalities. Respiratory involvement has always been conspicuously mild, and the episodes of arthropathy have not coincided with any changes in his respiratory status. At the onset of arthropathy the respiratory pathogens were *Staphylococcus aureus* and *Haemophilus influenzae.*

At the age of 11 years the joint symptoms became more severe and persistent, and there was a poor response to non-steroidal anti-inflammatory agents. A synovial biopsy of the knee showed a dark red synovial membrane. The histology is described in a later section. Prednisolone, in a dose of 10 mg daily, controlled the arthritis but attempts to lower the dose led to recurrence of symptoms. After seven months of corticosteroid treatment, hepatomegaly, hand tremor and personality changes developed and were attributed to the corticosteroids which were discontinued. Residual intermittent joint symptoms continued for a year. There were few joint symptoms between the ages of 14 and 16 years.

At the age of 16 there was an episode of benign intracranial hypertension which resolved spontaneously. Later, a massive gastrointestinal haemorrhage occurred. This was attributed to ibuprofen, which had been given in a dosage of 200 mg four times a day for some mild joint symptoms, and ibuprofen was discontinued (investigations excluded oesophageal varices or duodenal ulcer). Intermittent joint symptoms continued, and were later accompanied by depression (not attributed to the arthritis) and two episodes of parasuicide. The patient is now 26 years old, he has been free from joint symptoms for over two years, and there are no residual joint signs.

Case 2: Presented with pneumonia and failure to thrive at the age of 6 months. At the age of 11 years she complained of persistent pain in the right wrist and shoulder. A year later, both knees became red and swollen for five weeks, and effusions were present for six months. At this time the rheumatoid factor was weakly positive, the IgG, IgA and IgM were normal, and no complement studies were done. Radiographs showed no periosteal or other changes. This patient's respiratory problems have always been mild and at the onset of arthritis the sputum pathogens were *Staphylococcus aureus* and *Haemophilus influenzae.* At the age of 15, episodes of knee swelling occurred once or twice a week and lasted only a few hours. At the age of 19, she had recurrent swelling of the knees and fingers with stiffness of the elbows and wrists. The patient is now 22 years old and is free from joint symptoms and signs.

Case 3: He was shown to have CF at the age of 3 months, following three lower respiratory infections. Respiratory involvement has been moderately severe, but temporally

Table 1. Some clinical and laboratory details in patients with cystic fibrosis arthritis (CFA)[2-18]

No.	Sex	Age	Respiratory status	Rash	Immunoglobulins (IgA, IgG, IgM)	Complement	Joint involvement	RhF
1	M	6	?	Yes	IgA normal	CH50 92%	Monoarticular	Neg
2	M	2	?	Yes	IgA low, IgE high	?	Polyarticular	Neg
3	M	4	?	Yes	IgA low, IgE normal	?	Polyarticular	Neg
4	F	3	?	Yes	IgA, IgE normal	?	Monoarticular	Neg
5	F	10	?	Yes	?	?	Polyarticular	Neg
6	F	14	?	Yes	?	?	Ankle & others	?
7	F	11	Good	Yes	Normal	C1q 18.8%	Knees, wrists, PIP	Neg
8	F	8	Mod	No	Normal	C1q 20.4%	Hip	Neg
9	F	6	Good	Yes	?	?	Ankle	Neg
10	M	28	Good	No	?	?	Knees, elbows, shoulders	Neg
11	F	11	Good	Yes	Normal	?	Wrists, ankles	Neg
12	F	3	Mod	No	IgE slightly high	?	Knee	Neg
13	M	11	Good	No	IgG high	?	Knees, ankles, wrists, shoulders	Neg
14	F	23	Poor	Yes	IgG high	C1q 24%	Knees	WP
15	F	5	Good	No	Normal	?	Knees, ankle	Neg
16	M	5	Poor	Yes	Normal	?	Knees, ankle	Neg
17	F	5	Poor	No	Normal	?	Hip	Neg
18	?	?	?	?	?	?	Knees	?
19	?	?	?	?	?	?	Knees	?
20	?	?	?	?	?	?	Knees	?
21	?	?	?	?	?	?	Knees	?
22	?	?	?	?	?	?	Knees	?
23	M	24	?	No	?	?	Elbows	Pos
24	M	15	?	No	Normal	?	MTP	WP
25	F	17	?	No	IgG high	?	Knee	Neg
26	M●	9	Good	No	Normal	■	Knees, wrists, shoulders, MCP	Neg
27	F●	12	Good	No	Normal	?	Knees	Neg
28	M●	12	Good	Yes	Normal	?	Ankles	Neg
29	M●	12	Poor	No	Normal	Normal	Knees	Neg

●=present report
■=see case 1, present report
Mod=moderately severe
RhF=rheumatoid factor
PIP=proximal interphalangeal joints
MTP=metatarsophalangeal joints
MCP=metacarpophalangeal joints
WP=weakly positive

Table 2. Further observations and investigations in patients with cystic fibrosis arthritis (CFA)[2-18]

Number of informative patients	Observation/investigation
16	Finger clubbing in all 16
22	Pancreatic enzymes taken in 20
11	Haemoglobin range 12.0-14.3 g/dl
19	ESR range 1-33 mm/hr
10	White cell count range $6.2\text{-}19.2\times10^3$
17	Serum uric acid normal
11	Serum amylase normal
12	Anti-streptolysin titre normal in 9; 50-200 in 3 patients
4	Brucella, salmonella, mycoplasma antibodies negative
8	HLA antigens: 2 patients were B27 CW2 positive

unrelated to the arthritis. At the age of 7 years the first episode of painful swelling of the left knee occurred. This was not associated with systemic upset and lasted four days. There were no skin rashes. Initially, recurrences were at monthly intervals but became less frequent. At 9 years, the right knee became similarly affected and has subsequently been the most severely affected joint. Over the last few months there has been painful swelling of the right knee every 4-6 weeks, lasting for 2-3 days. Some relief has been obtained with aspirin. Between acute episodes a small effusion persists in the right knee joint, and there is quadriceps wasting on that side. The serum levels of IgG, IgA, IgM, uric acid and amylase were normal, rheumatoid factor negative, C1q 120% (normal), C_3 1.48 g/l (normal 0.8-1.4), C_4 0.29 g/l (normal 0.2-0.4) and the patient was HLA A3, A31, B7, B27, CW2. Radiographs show no abnormality other than the joint effusion, and a ^{99m}Tc bone scan was normal. *Pseudomonas aeruginosa* has recently been isolated from the sputum.

Case 4: This boy presented with vomiting, failure to thrive, and pneumonia, and CF was diagnosed at the age of 6 weeks. He had several lower respiratory illnesses in the first 7 years, but subsequently has had infrequent chest problems. Now aged 15½ years, he is pubertal. The pathogens in his sputum are *Staphylococcus aureus* and *Haemophilus influenzae*. Psoriasis was first noted at 9 years of age, but has always been mild, with small patches of affected skin on the back and scalp. Nail-pitting has been noted in the past. There was a sudden onset of arthritis at the age of 12, with swelling, redness and pain in the left ankle but no systemic disturbance or rash. He was treated with antibiotics because of a suspicion of septic arthritis, and the symptoms and signs

Table 3. Clinical details of CF patients with purpura

No.	Age	Sex	Respiratory status	Joints affected	Site of purpura	Immunoglobulins (mg/dl) IgG	IgA	IgM	Years to death	Clq	RhF
1	6	F	Mild	Ankle	Legs	?	?	?	?	?	Neg
2	23	F	Severe	Knees	Legs	2500	N	N	1	24%	Pos
3	16	M	Severe	Ankles	Legs	3800	680	310	2	54%	Neg
4	?	F	Severe	None	Legs	?	?	?	2	?	?
5	20	M	Severe	Ankles	Feet & finger	2280	520	360	7/12	?	?
6	20	?	Severe	None	Legs	2520	422	94	1½	?	?
7	14	?	Severe	None	Legs	2670	479	39	5/12	?	?
8	14	M	Severe	None	Legs	3510	119	47	6/12	?	?
9	17	?	Severe	None	Legs	2170	432	95	?	?	?

RhF=Rheumatoid factor; N=Normal value

disappeared in three days. At this time the rheumatoid factor was negative, the serum levels of IgG, IgA, IgM and uric acid were normal, the ESR was 13 mm/h, and the patient was HLA A9, A11, B27, B37, CW2. Radiography of the long bones was normal and showed no periosteal new bone formation.

Over the next two years he had recurrent episodes of swelling and pain in both ankles, initially at three-weekly intervals but becoming less frequent and less severe. Each episode lasted 3-4 days. At the age of 15, he had a further episode of severe swelling of the left ankle and lower leg. An erythematous non-purpuric rash was noted around the ankle, and the skin of the lower leg desquamated when the swelling subsided. On examination four months later there are no residual signs or symptoms.

The clinical details and the results of investigations for all 29 patients with CFA are shown in Tables 1 and 2. The condition appears to occur at any age past infancy, and the mean age at which the condition was first noted was 10.6 years overall, males 11.8 years and females 9.7 years. There was a small excess of females, the male to female ratio being 0.85.

Although sometimes preceded by vague pains, the onset of CFA is usually sudden, with one or more acutely inflamed, swollen, painful joints in an otherwise well patient, occasionally accompanied by a low-grade fever. A diagnosis of cellulitis or septic arthritis has been entertained in some patients, but cultures of blood and synovial fluid are sterile. Symptoms and signs disappear either spontaneously or with the aid of non-steroidal anti-inflammatory agents within a few days to weeks, only to recur in most patients within a few weeks or months. The joints most commonly affected are the knees and ankles. There is no temporal relationship between the appearance of joint lesions and pulmonary disease. The radiological appearances, apart from demonstrating any effusion, are usually normal, and there are no erosions of the joint surfaces.

Eleven patients with CFA were reported to have a rash, usually coinciding with joint symptoms. This was usually a maculopapular, erythematous rash, usually in the vicinity of an affected joint, but occasionally it was more widespread. Three patients had an erythema nodosum-like rash and two had a purpuric rash on the legs. One of these, patient 14 in Table 1, is reminiscent of two patients from Boston[19] with purpura associated with hypergammaglobulinaemia and arthralgia particularly of the ankles. Histology of the skin in these two patients showed necrotizing vasculitis. Among a series of 156 patients with CF in Copenhagen, four further cases of purpura and hypergammaglobulinaemia were found[20] (none had arthritis). The clinical and laboratory features of 9 such patients are summarized in Table 3. In 8 out of 9 cases, the purpura never occurred more than two years before death, suggesting that this sign heralds a poor outcome.

Hypertrophic pulmonary osteoarthropathy

Case 5: This boy presented with pneumonia and failure to thrive, and CF was diagnosed at the age of 4 months. There were frequent respiratory infections, and from the age of 10 years he had exercise dyspnoea and persistent crepitations. At the age of 16, he developed pain and swelling in the left knee followed by the same symptoms in the right knee. Both knees were very swollen, and there were also pains in the arms and wrists. Symptoms were intermittent at first. At the age of 17, when respiratory infection was severe, joint symptoms became persistent. During his last illness joint symptoms again became prominent. Investigations showed: IgG 31.5 g/l (elevated), IgA 11.0 g/l (elevated), IgM 2.7 g/l (normal). Radiographs showed periosteal new bone formation in the left fibula. The patient died of respiratory failure at the age of 18. At necropsy, histology showed periosteal destruction and new bone formation, characteristic of HPOA. The synovial membrane was normal apart from slightly increased vascularity.

Details of the 22 patients with HPOA are summarized in Table 4. The mean age at presentation was 15.1 years overall, females 12.4 years, males 19.8 years. The male to female ratio was 2.0. A comparison of the features of HPOA and CFA is given in Table 5.

The diagnosis of HPOA is made on detecting periosteal changes in long bones using conventional radiology or isotopic bone scanning[21]. Joint effusions, often very large, are a frequent radiographic feature, but HPOA may be clinically silent, the diagnosis being made when patients with severe lung disease are screened with long bone radiographs[4]. Tenderness and swelling of the affected limb (usually the leg) may occur. Gynaecomastia (in males) and mastalgia (in women) occur in a minority of patients, varying with the joint changes[14].

The mean and median ages of those with HPOA are higher than those with CFA, and reflect the fact that HPOA is confined to those patients with severe lung disease. A striking feature of HPOA is how changes in joint symptoms closely follow changes in the respiratory state. In these patients, joint and bone symptoms relapsed with acute pulmonary deterioration, but improved when the patient was treated with antibiotics. The underlying radiological changes do not vary in this way[14].

Table 4. Clinical details of patients with CF and hypertrophic pulmonary osteoarthropathy (HPOA)

No.	Age at Onset HPOA	Age at Death	Sex	Respiratory status	Joints affected	Periosteal changes on radiographs	Temporal correlation with chest relapse	Treatment of HPOA
1	10	11	F	Poor	Knees, ankles	Present	Yes	None
2	14	?	M	Mod	Knees, ankles	Present	Yes	None
3	15	17	F	Poor	Knees	Present	Yes	None
4	24	?	M	Poor	Knees, ankles, wrists	Present	?	Paracetamol, indomethacin
5	23	?	M	Poor	Knees, ankles	Present	?	Paracetamol
6	21	?	M	Poor	Knees, ankles	Present	?	Paracetamol, indomethacin
7	10	12	F	Poor	Knees, ankles, wrists	Present	?	?
8	7	9	F	Poor	Knees, ankles, wrists	Present	Yes	None
9	20	?	?	Poor	None	Present	?	None
10	15	?	?	Poor	None	Present	?	None
11	13	13	?	Poor	None	Present	?	None
12	21	?	M	Poor	Knees, ankles, wrists	Present	Yes	?
13	15	?	M	Mod	None	Present	?	None
14	21	?	M	Poor	Knees, ankles	Present	Yes	None
15	22	?	M	Mod	Knees, ankles	Present	Yes	None
16	25	?	?	Poor	Knees, ankles, wrists	Present	Yes	None
17	30	?	M	Poor	Knees, ankles	Present	Yes	None
18	30	?	F	Mod	Knees, ankles	Present	Yes	None
19	18	?	M	Mod	Knees, ankles	Present	No	?
20	22	?	M	Mod	Knees, ankles	Present	No	?
21●	16	18	M	Poor	Knees, ankles, wrists, elbows	Present	Yes	Flurbiprofen, paracetamol, indomethacin
22	7	?	F	Poor	?	Present	?	?
23	8	?	F	Poor	Knees	Absent	Yes	None
24	5	?	M	Poor	Ankles	Present	?	?

●=present report

Table 5. Comparison of the features of cystic fibrosis arthritis (CFA) and hypertrophic pulmonary osteoarthropathy (HPOA) in CF

	CFA	HPOA
Mean age (years)	10.6 (M 11.8, F 9.7)	15.1 (M 19.8, F 12.4)
Median age (years)	11	18
Age range (years)	2-28	7-30
Sex (M/F)	11/13	14/7
Respiratory status:		
Good	9	0
Moderate	2	6
Poor	4	18
Rash/nodules	12/24 (50%)	4/23 (18%)
Joints affected	Knees, ankles, wrists	Knees, ankles
Temporal relationship to lung disease	None	Close
Clubbing	18/18 (100%)	20/20 (100%)
Pseudomonas in sputum	10/19 (53%)	6/6 (100%)
Gynaecomastia	–	4/8 (50%)
Died within 3 years of onset of arthropathy	2/29 (7%)	6/21 (29%)

Note: the figures in this table are based on the number of informative cases

Histology of CFA

A synovial membrane biopsy was taken from Case 1 at the age of 9 years. Haematoxylin and eosin staining showed increased vascularity in the synovial membrane. A number of granulomas were seen, comprising collections of mononuclear cells with a few multinucleated giant cells. The granulomas were surrounded by large numbers of lymphocytes. This appearance is characteristic of that seen in sarcoid or chronic granulomatous disease. The latter is a condition which, like CF, results in the presence of chronic bacterial antigenic stimulus. More recently, an immunoperoxidase preparation of this tissue shows the presence of a moderate number of plasma cells containing IgG.

Pathogenesis of CFA

Several attempts have been made to find a model for CFA in other diseases in which arthritis is a complication. These are briefly discussed, together with other theories on pathogenesis.

Inflammatory bowel disease

Arthritis is associated with inflammatory bowel disease, the incidence varying from less than 1% in dysentery to about 20% in Crohn's disease[22]. Enteropathic arthritis resembles CFA in that it principally affects large joints, especially the knees and ankles, and both conditions may be accompanied by erythema nodosum[23]. As in CFA, the arthritis in chronic inflammatory bowel disease does not cause radiological evidence of joint surface destruction, but the synovial histology shows a nonspecific inflammatory reaction. A patient with both Crohn's disease and CF who had arthritis has been reported[16].

Jejunoileal bypass

A report of 8 cases of CFA from Philadelphia[15] pointed out a similarity to the arthritis/dermatitis syndrome which commonly follows jejunoileal bypass

creation. A study of this phenomenon in 13 patients noted that the knees were the most frequently affected joints, followed by the wrists and the metacarpophalangeal joints[24]. The duration of each episode was 3-30 months, considerably longer than the few days or weeks seen in CFA. Three of the 13 patients with post-bypass arthritis had a rash on the shins that was clinically indistinguishable from erythema nodosum. Histology of the skin lesions showed mild, chronic inflammation with notably no vasculitis or fatty necrosis[24]. Immune complexes have been detected in the serum of post-bypass patients[25], but it appears that these are equally common in those with or without arthritis[24]. Minimal perivascular deposits of IgA and C3 were seen on immunofluorescent staining at synovial biopsy. There are some clinical and laboratory similarities between CFA and post-bypass patients. In both situations there is a source of chronic antigenic stimulus with incomplete absorption of food.

Cimetidine

Synovitis, joint swelling and joint effusion can occur as adverse reactions to cimetidine, which has been used in some patients with CF to facilitate the action of pancreatic enzymes.

Pancreatitis

Skin lesions resembling erythema nodosum associated with arthritis have been described in pancreatitis[26], but the lesions have been diagnosed histologically as being caused by fat necrosis, which has not been documented in CF.

Rheumatoid arthritis

The joint lesions of CFA can be distinguished from those of juvenile rheumatoid arthritis by the more remitting course of the former and the absence of radiological evidence of joint destruction[27].

Six patients with joint symptoms and CF have had a positive serum rheumatoid factor, usually of low titre[8,17]. Two of these patients and an additional child[9] appear to meet the currently accepted criteria for diagnosing rheumatoid arthritis. The emergence of a positive serum rheumatoid factor test in patients with chronic inflammatory states has been noted[28], but, perhaps surprisingly, CF patients in general do not have a higher incidence of rheumatoid factor than control populations[29].

Hyperuricaemia

Both hyperuricosuria[30,31] and hyperuricaemia[32] have been demonstrated in patients with CF who are taking high dosages of pancreatic extracts. There is a real risk of uric acid nephropathy, but none of the reported patients had joint manifestations. A normal serum uric acid level in patients with CFA excludes gout as the cause of the arthritis.

Infections

Various microorganisms, including several cocci and viruses[27], are classically associated with polyarthritis. *Mycoplasma pneumoniae* is an infecting organism which can occur in CF[33], and it too can be associated with an arthritis[34]. However, the prolonged course of CFA is inconsistent with the transient migratory polyarthritis associated with *Mycoplasma pneumoniae* infection.

'Hyperimmune' theory of CFA

Much interest has centred on the theory that an abnormal immune reaction may be partly responsible for the lung damage in CF. Further, it has been suggested that CFA may be attributable to the deposition of immune complexes in the synovial membrane[35]. Circulating immune complexes have been demonstrated in the serum and sputum of CF patients[36-39]. Deposits of immunoglobulins and immune complexes have been seen in many organs at necropsy, although these findings are not specific for CF[39]. Serum precipitins to *Pseudomonas aeruginosa* have been demonstrated[40], and high titres have been shown to be associated with a poor prognosis[41]. It is possible that these abnormalities are secondary effects of chronic infection[40].

In diseases where arthritis is a primary feature, such as rheumatoid arthritis or systemic lupus erythematosus, immunological abnormalities are prominent[42]. A further notable feature of some connective tissue disorders is the association with certain HLA antigens. HLA antigens were sought in only 8 patients with CFA, and, interestingly, 2 were HLA B27 CW2 positive. An immunological mechanism in the pathogenesis of CFA seems possible, in view of *(a)* the strong association between immunologically mediated disease and arthropathy, *(b)* the evidence that hyperimmune processes occur in CF[43], *(c)* the high incidence of associated skin rashes in CFA (and this combination is again characteristic of connective tissue disorders), and *(d)* support provided by the histological findings in Case 1 (see above) of this report.

Pathogenesis of hypertrophic pulmonary arthropathy

Finger-clubbing and HPOA used to be considered different degrees of the same pathological process. It is now thought that they are separate processes with many common features[44]. In CF, finger-clubbing, often gross, is almost universal eventually, and yet HPOA is rarely noted.

A major (but not essential) feature of HPOA is radiological evidence of periosteal new bone formation, and the radiological signs of HPOA may be present without clinical symptoms[14]. Less commonly, the clinical features may occur without radiological changes[45]. Increased vascularity and oedema of the periosteum, ligaments, tendons and subcutaneous tissue are the principal initial pathological changes. New bone is laid down outside the original cortex and non-inflammatory synovial effusions may develop. No evidence of a pathogenic role for immune complexes was found in a study of 3 patients with HPOA[46].

The pathogenesis of HPOA is obscure. In childhood, it has been found in association with conditions as diverse as chronic liver disease, skeletal tuberculosis and thymic neoplasm, as well as chronic pulmonary disease and cyanotic congenital heart disease[47]. Symptomatic relief can be obtained by vagotomy[48] without removal of the underlying disease. Cure of the underlying disease usually results in the disappearance of HPOA, and it is worth noting that patients with CF who have HPOA show a close correlation between the severity of arthritic symptoms and the severity of pulmonary involvement. Pulmonary tumours associated with HPOA are usually near the pleura[49] suggesting that

afferent vagal pathways, if they exist, are pleural in origin.

In view of the increased blood flow to the affected limbs, a role for a chemical vasodilator has been proposed as the efferent pathway following vagal stimulation[14]. In addition, increased oestrogen levels have been sought in HPOA in view of the frequency of gynaecomastia. Normal oestrogen levels have been found in HPOA associated with hepatic disease[50]. Raised oestrogen levels were found in another study, but the patients with the higher levels were not the ones with gynaecomastia[51]. Finally, the improvement of pain and swelling in HPOA during treatment with indomethacin points to a role for prostaglandins which can increase and activate osteoclasts and increase bond resorption[52].

Investigations and treatment

As has been shown above, the diagnosis of CFA is one of exclusion unless a synovial biopsy is performed, but this is not routinely recommended. HPOA may require an isotopic bone scan for diagnosis, and both conditions need a deeper understanding of pathogenesis than we have at present. A suggested list of investigations which are required is given below:

Joint and long bone radiographs	Amylase
^{99m}Tc bone scan	HLA antigens
Full blood count	Brucella titre
Sedimentation rate	C3, C4, C5,
Rheumatoid factor	CH50, C1q
Antinuclear factor	IgA, IgG, IgM, IgE
Uric acid	Liver function tests

Treatment is hardly mentioned in published reports of CFA. Local experience is that non-steroidal anti-inflammatory agents such as ibuprofen or indomethacin are usually helpful, though we have experienced one episode of massive gastrointestinal haemorrhage due to ibuprofen, a side effect which is claimed to be very rare. Since CFA tends to remit spontaneously, treatment may not be needed for long periods. Some patients with CF have liver disease causing either a bleeding diathesis or oesophageal varices, and in these patients aspirin is contra-indicated. Aspirin, especially in slow-release form, may be a particular hazard in CF where the buffering capacity of intestinal bicarbonate is absent and erosions and haemorrhage may result[52]. Systemic corticosteroids are likely to be effective, as in Case 1, and used for a few months have a role in patients unresponsive to non-steroidal anti-inflammatory agents. A particular risk in adolescent and adult CF patients when using corticosteroids is the possibility of precipitating diabetes mellitus. Intra-articular corticosteroids might be useful in pauci-articular disease, though there is no local experience of this.

HPOA is best treated by removal of the underlying cause or by vagotomy. The former is unattainable at present, and the latter would subject the CF patient, who almost certainly has advanced lung damage, to the hazards of an anaesthetic and surgery. An inflammatory reaction is not characteristic of HPOA, so analgesics are likely to be the mainstay of treatment. Aspirin has been shown to be helpful[49] and, more recently, the use of indomethacin has been claimed to result in dramatic relief of pain and swelling[53].

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